REMARKS

Claims 1-29 are currently pending. Claims 24-29 have been withdrawn as directed to a non-elected invention. The present Response cancels claim 9; amends elected claims 1, 4 and 10; amends withdrawn claims 24 and 28; and adds new claim 30.

I. Claim Amendments

Claim 1 has been amended to specify that "the pregelatinized starch exhibits (a) a shear stress of not more than about 1 Pa at a shear rate of 20 s^{-1}, and (b) optionally, a multimodal particle size distribution." Support for this amendment can be found, for example, in original claims 9 and 18; and at paragraphs [0040] and [0043] of the specification.

Claim 4 has been amended to correct typographical mistakes introduced by a prior amendment. Support for this amendment can be found, for example, in original claim 4; and at paragraph [0029] of the specification.

Claim 10 has been amended to correct (a) the claim dependency in view of the cancellation of the claim from which it depends, and (b) the misspelling of the word "pregelatinized."

Claim 24 has been amended to specify that the pregelatinized starch exhibits "(a) a shear stress of not more than about 1 Pa at a shear rate of 20 s^{-1}, and (b) optionally, a multimodal particle size distribution." Support for this amendment can be found, for example, in original claims 9 and 18; and at paragraphs [0015], [0040], and [0043] of the specification.

Claim 28 has been amended to specify that the pregelatinized starch exhibits "(a) a shear stress of not more than about 1 Pa at a shear rate of 20 s^{-1}, and (b) optionally, a

multimodal particle size distribution." Support for this amendment can be found, for example, in original claims 9 and 18; and at paragraphs [0014], [0040], and [0043] of the specification.

New claim 30 depends from claim 1 and further specifies a test procedure used to determine the shear stress of the pregelatinized starch. Support for this amendment can be found, for example, at paragraph [0037] of the specification.

II. Section 102(a)/102(e) Rejection

The Office rejected claims 1-23 under 35 U.S.C. §102(a) and §102(e) as being anticipated by US2002/0013357 (the "Nadkarni 2002 Reference"). More specifically, the Office has asserted:

> Nadkarni et al. disclose pharmaceutical compositions containing from about 1 mg to about 100 mg of valdecoxib useful in treatment of cyclooxygenase-2-mediated conditions and disorders (Abstract). Nadkarni et al. disclose that the tablet compositions contain pregelatinized starch (National Starch 1500: a **corn starch**) in the same amount, 20 mg, as the instant application (Page 8, Tables 1 and 2 and claims 1, 4, 6 and 7). Applicant teaches the same pregelatinized starch in the tablet (instant specification, page 21 Table 1). **It is the Examiner's position that since the same pregelatinized starches are taught in the same amount then the tablet disclosed by Nadkarni et al. would have low viscosity and/or exhibit a multimodal particle size distribution and read on instant claims 1-6, 17 and 19.**
>
> * * *
>
> Instant claims 9-17 are directed to shear stress values for the pregelatinized starch. Since the disclosure of Nadkarni et al. teaches the exact same pregelatinized starch in the exact same amount as the instant application, then **it is the Examiner's position, without evidence to the contrary, that the pregelatinized starch of the disclosure of Nadkarni et al. inherently has those properties.**
>
> * * *
>
> Applicant asserts that the cited references do not disclose selection of the pregelatinized [sic] starch on the basis of determination of low viscosity and/or a particle size test. The claim as currently amended now reads on a product by process. As stated above, the patentability of the product does not depend on its method of production. The Examiner has found a product made with pregelatinized starch. It is noted that Applicant is also using Starch 1500 supplied by Colorcon (page 21, table 1 [0081]). **It appears as if Nadkarni et al. and Applicant are using the same corn starch.**

April 7, 2008 Office Action, pages 3-5 (emphasis added).

The present application addresses a formulation problem encountered with conventional pharmaceutical oral dosage forms containing a drug of low solubility and a pregelatinized starch---undesired variability in the dissolution rate of such dosage forms. Applicants have discovered that incorporating a starch having the required physical property (i.e., a pregelatinized starch that exhibits (a) a shear stress of not more than about 1 Pa at a shear rate of 20 s^{-1}, and (b) optionally, a multimodal particle size distribution) in the formulation used to prepare such dosage forms materially reduces the variability in the dissolution rate of those dosage forms relative to conventional pharmaceutical oral dosage forms that do not employ a pregelatinized starch having the required physical property.

Claim 1 (the sole pending independent claim) as amended now specifies that the pregelatinized starch used in the formulation has this nonobvious, required physical property:

> 1. An orally deliverable pharmaceutical composition comprising a drug of low water solubility and a pregelatinized starch, **wherein the pregelatinized starch exhibits (a) a shear stress of not more than about 1 Pa at a shear rate of 20 s^{-1}, and (b) optionally, a multimodal particle size distribution.**

Claims 2-23 all depend, directly or indirectly, from claim 1 and incorporate the limitations of claim 1.

The Office has not established a *prima facie* case of anticipation with respect to the claims as amended. While disclosing pharmaceutical compositions containing pregelatinized starch generally, the Nadkarni 2002 Reference is completely silent on the shear stress and particle size distribution properties exhibited by the pregelatinized starch used in the pharmaceutical composition. The Nadkarni 2002 Reference simply does not teach or suggest using a pregelatinized starch exhibiting the desired shear

stress or a multimodal particle size distribution, to reduce variability in dosage form dissolution rate or otherwise.

Assuming, *arguendo*, however, that the Office has stated a *prima facie* case of anticipation, applicants already have presented evidence that effectively rebuts that *prima facie* case. The examples presented in the application specifically confirm the variability in (a) the physical properties of pregelatinized starch from different manufacturing lots, and (b) the physical properties of tablets prepared from different manufacturing lots of pregelatinized starch:

(1) Example 2 reports the results of an *in vitro* dissolution test on eleven tablets prepared from eleven different manufacturing lots (Lots A-K) of Starch 1500, a pregelatinized starch obtained from Colorcon. These results reflect a material variation in the percent dissolution of the tablets prepared from the different manufacturing lots, with three of the eleven tablets failing to achieve the percent dissolution target.

(2) Example 3 reports that six of the pregelatinized starch manufacturing lots described in Example 2 (Lots B, C, G, H, J and K) were tested in accordance with the procedure described in paragraph [0037] of the specification (and also specified in new claim 30) to determine whether the starches were "low viscosity" starches. Two (Lots J and K) of the six starches did not qualify as "low viscosity" starches. Tablets prepared with the pregelatinized starch of low viscosity (Lots B,C, G, and H) passed the *in vitro* dissolution test of Example 2 while the otherwise identical tablets prepared with the pregelatinized starch not meeting the low viscosity criterion (Lots J and K) did not pass the dissolution test.

(3) Example 4 reports that the eleven pregelatinized starch manufacturing lots described in Example 2 (Lots A-K) were tested to determine particle size distribution. Eight of the eleven pregelatininzed starch lots (Lots A-H) exhibited a bimodal particle size distribution. Three of the eleven pregelatininzed starch lots (Lots I-K) exhibited a unimodal particle size distribution. Tablets prepared with pregelatinized starch

exhibiting a bimodal particle size distribution (Lots A-H) passed the *in vitro* dissolution test of Example 2 while the otherwise identical tablets prepared with pregelatinized starch exhibiting a unimodal particle size distribution (Lots I-K) did not pass the dissolution test.

In addition, this variability in the properties of starches was well-known in the art at the time the present application was filed:

> Starches from different plant sources differ in their amylose/amylopectin ratio. For example, corn starch contains about 27% amylose, potato starch about 22%, and tapioca starch about 17%. In contrast, waxy corn starch contains almost entirely amylopectin, with no amylose. **These differences modify the physical properties of the starches such that the various types may not be interchangeable in a given pharmaceutical application.** For example, amylose-rich maize starch has been studied as a potential tablet film-coating ingredient

Handbook of Pharmaceutical Excipients, Fourth Edition (Raymore C. Rowe, Editor), p. 608 (2003) (emphasis added). A copy of pages 603-614 of this Handbook of Pharmaceutical Excipients is attached to this Response for the convenience of the Office.

Further, the present rejection does not even comply with the Office's own requirements for a showing of inherency. The Office has expressly acknowledged that inherency is not established by mere possibilities:

> **The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.** *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) . . .
>
> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that **the allegedly inherent characteristic necessarily flows from the teachings of the**

applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) . . .

MPEP 2112(IV) (emphasis added). As discussed above, the specific examples in the pending application confirm that all pregelatinized starches do not inherently exhibit (a) a shear stress of not more than about 1 Pa at a shear rate of 20 s^{-1}, and (b) a multimodal particle size distribution. Further, those of ordinary skill in the art recognize that starches can have different physical properties and that different starches are not necessarily interchangeable in pharmaceutical compositions.

Finally, applicants expressly disagree with the Office's characterization of the claims as product-by-process claims. The claims as amended clearly are composition claims and not product-by-process claims.

Accordingly, claims 1-23 are not inherently anticipated by the Nadkarni 2002 Reference and the Office should withdraw the present §102(a)/§102(e) rejection.

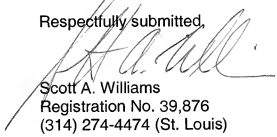
III. Section 102(b) Rejection

The Office also rejected claims 1-23 under 35 U.S.C. §102(b) as being anticipated by WO01/41761 (the "Nadkarni 2001 Reference"). The Nadkarni 2001 Reference and the Nadkarni 2002 Reference appear to be substantially the same, if not identical, disclosures. The arguments by the Office in support of this §102(b) rejection are identical to the arguments by the Office in support of the §102(a)/§102(e) rejection previously discussed above. See April 7, 2008 Office Action, pages 5-7.

Accordingly, for the same reasons presented above with respect to the §102(a)/§102(e) rejection, claims 1-23 are not inherently anticipated by the Nadkarni 2001 Reference and the Office should withdraw the present §102(b) rejection.

Applicants respectfully submit that the present application is in condition for allowance. To advance the prosecution of the present application, however, the Office is invited to contact the undersigned at the telephone number provided below. If any additional fees are required or an overpayment of fees is made, however, the Office is authorized to debit or credit our Deposit Account No. 16-1445, as necessary.

Respectfully submitted,



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Handbook of Pharmaceutical Excipients

FOURTH EDITION

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2003002641

Starch

1 Nonproprietary Names

BP: Maize starch
Potato starch
Rice starch
Tapioca starch
Wheat starch

JP: Corn starch
Potato starch
Rice starch
Wheat starch

PhEur: Maydis amylum (maize starch)
Solani amylum (potato starch)
Oryzae amylum (rice starch)
Tritici amylum (wheat starch)

USPNF: Starch

Note that the USPNF 20 describes starch, in a single monograph, as being obtained from either the mature grain of corn, *Zea mays*, or of wheat, *Triticum aestivum*, or from tubers of the potato, *Solanum tuberosum*, or of tapioca, *Manihot utilissima*. The PhEur 2002 has individual monographs for each of these starches, except for tapioca starch, along with an additional monograph for rice starch, *Oryza sativa*. The BP 2001 similarly describes maize, potato, rice, tapioca (cassava), and wheat starch in individual monographs, tapioca starch being obtained from the rhizomes of *Manihot utilissima* Pohl. The JP 2001 similarly describes corn (maize), rice, potato and wheat starch in separate monographs. *See also* Section 18.

2 Synonyms

Amido; amidon; amilo; amylum; *Aytex P*; *Fluftex W*; *Instant Pure-Cote*; *Melojel*; *Meritena*; *Paygel 55*; *Perfectamyl D6PH*; *Pure-Bind*; *Pure-Cote*; *Pure-Dent*; *Pure-Gel*; *Pure-Set*; *Purity 21*; *Purity 826*; *Tablet White*.

See also Sections 1 and 18.

3 Chemical Name and CAS Registry Number

Starch [9005-25-8]

4 Empirical Formula and Molecular Weight

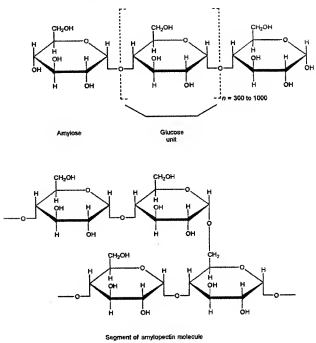
$(C_6H_{10}O_5)_n$

Molecular Weight: 50 000–160 000

where n = 300–1000.

Starch consists of amylose and amylopectin, two polysaccharides based on α-glucose. *See also* Sections 5 and 17.

5 Structural Formula



6 Functional Category

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.[1]

In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w.[2–9] However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In

granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation. Also starch when used as a disintegrant exhibits type II isotherms and has a high specific surface for water sorption.[10]

Starch has been investigated as an excipient in novel drug delivery systems for nasal,[11] oral,[12,13] peridontal,[14] and other site-specific delivery systems.[15]

Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

Therapeutically, rice starch-based solutions have been used in the prevention and treatment of dehydration due to acute diarrheal diseases.

8 Description

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–6.5 for a 2% w/v aqueous dispersion of corn starch, at 25°C.

Compressibility: *see* Figure 1.

Density (bulk): 0.462 g/cm^3 for corn starch.

Density (tapped): 0.658 g/cm^3 for corn starch.

Density (true): 1.478 g/cm^3 for corn starch.

Flowability: 10.8–11.7 g/s for corn starch;[9] 30% for corn starch (Carr compressibility index).[16] Corn starch is cohesive and has poor flow characteristics.

Gelatinization temperature: 73°C for corn starch; 72°C for potato starch; 63°C for wheat starch.

Moisture content: all starches are hygroscopic and rapidly absorb atmospheric moisture.[17,18] Approximate equilibrium moisture content values at 50% relative humidity are 11% for corn starch; 18% for potato starch; 14% for rice starch; and 13% for wheat starch. Between 30% and 80% relative humidity, corn starch is the least hygroscopic starch and potato starch is the most hygroscopic. Commercially available grades of corn starch usually contain 10–14% water. *See also* Figures 2 and 3.

Particle size distribution:
- Corn starch: 2–32 μm
- Potato starch: 10–100 μm
- Rice starch: 2–20 μm
- Tapioca starch: 5–35 μm
- Wheat starch: 2–45 μm

Median diameter for corn starch is 17 μm and for wheat starch is 23 μm.

Solubility: practically insoluble in cold ethanol (95%) and in cold water. Starch swells instantaneously in water by about 5–10% at 37°C.[2,18] Polyvalent cations produce more swelling than monovalent ions, but pH has little effect.

Specific surface area:
- 0.41–0.43 m^2/g for corn starch
- 0.12 m^2/g for potato starch
- 0.27–0.31 m^2/g for wheat starch

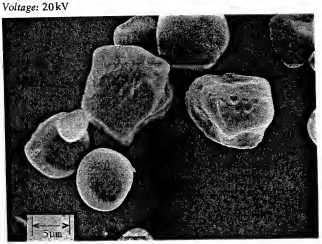
Swelling temperature:
- 65°C for corn starch
- 64°C for potato starch
- 55°C for wheat starch

Viscosity (dynamic): 13.0 mPa s (13.0 cP) for a 2% w/v aqueous dispersion of corn starch at 25°C.

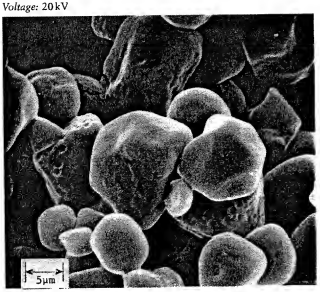
Table I: Pharmacopeiol specifications for storch.

Test	JP 2001	PhEur 2002	USPNF 20
Identificotion	+	+	+
Botanic characteristics	—	+	+
Microbial limits	—	+	+
pH			
Corn starch	—	—	4.5–7.0
Potato starch	—	5.0–8.0	5.0–8.0
Tapioca	—	—	4.5–7.0
Wheat starch	—	5.0–8.0	4.5–7.0
Acidity	—	+	—
Loss on drying			
Corn starch	⩽15.0%	⩽15.0%	⩽14.0%
Rice storch	⩽15.0%	⩽15.0%	—
Potato starch	⩽18.0%	⩽20.0%	⩽14.0%
Tapioca	—	—	⩽14.0%
Wheat storch	⩽15.0%	⩽15.0%	⩽14.0%
Residue on ignition	—	—	⩽0.5%
Sulfated ash			
Corn starch	⩽0.5%	⩽0.6%	—
Rice starch	⩽1.0%	⩽1.0%	—
Potato starch	⩽0.5%	⩽0.6%	—
Wheat starch	⩽1.0%	⩽0.6%	—
Iron			
Corn starch	—	—	⩽0.002%
Potato starch	—	⩽10 ppm	⩽0.002%
Tapioca starch	—	—	⩽0.002%
Wheot storch	—	⩽10 ppm	⩽0.002%
Orgonic volotile impurities	—	—	+
Oxidizing substances			
Corn storch	—	—	⩽0.002%
Potato starch	—	+	⩽0.002%
Tapioca starch	—	—	⩽0.002%
Wheat starch	—	+	⩽0.002%
Sulfur dioxide			
Corn starch	—	—	⩽0.008%
Potato starch	—	⩽50 ppm	⩽0.008%
Wheat starch	—	⩽50 ppm	⩽0.008%
Total protein			
Corn starch	—	—	—
Rice starch	—	—	—
Potato starch	—	⩽0.1%	—
Wheat storch	—	⩽0.3%	—
Foreign matter	—	+	—

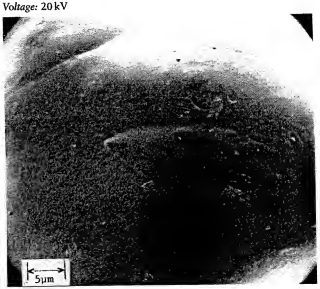
SEM: 1
Excipient: Corn starch
Manufacturer: Anheuser Busch
Lot No.: 96A-3 (67)
Magnification: 2400×
Voltage: 20 kV



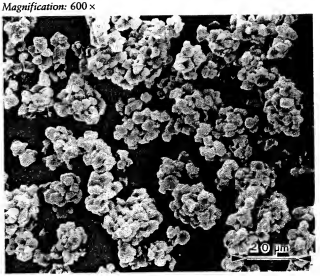
SEM: 2
Excipient: Corn starch
Manufacturer: AE Staley Mfg. Co.
Lot No.: 96A-4 (G77912)
Magnification: 2400×
Voltage: 20 kV



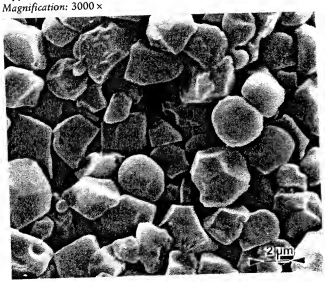
SEM: 3
Excipient: Potato starch
Manufacturer: Starchem
Lot No.: 96A-5 (1179)
Magnification: 2400×
Voltage: 20 kV



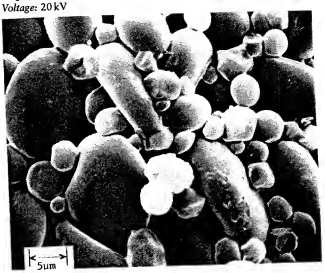
SEM: 4
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 600×



SEM: 5
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 3000 ×



SEM: 7
Excipient: Wheat starch (*Aytex P*)
Manufacturer: Henkel Corp.
Lot No.: 96A-2 (2919D)
Magnification: 2400 ×
Voltage: 20 kV



11 Stability and Storage Conditions

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties.

Starch should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

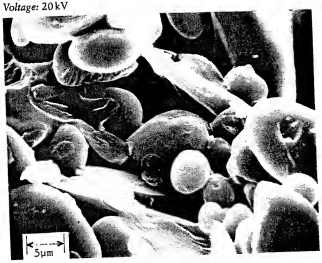
Starch is extracted from plant sources through a sequence of processing steps involving coarse milling, repeated water washing, wet sieving, and centrifugal separation. The wet starch obtained from these processes is dried and milled before use in pharmaceutical formulations.

14 Safety

Starch is widely used as an excipient in pharmaceutical formulations, particularly oral tablets.

Starch is an edible food substance and is generally regarded as an essentially nontoxic and nonirritant material.[19] However, oral consumption of massive doses can be harmful owing the formation of starch calculi, which cause bowel obstruction.[20] Starch may also cause granulomatous reactions when applied to the peritoneum or the meninges. Contamination of surgical wounds with the starch glove powder used by surgeons has also resulted in the development of granulomatous lesions.[21]

SEM: 6
Excipient: Wheat starch (*Paygel 55*)
Manufacturer: Henkel Corp.
Lot No.: 96A-1 (2917D)
Magnification: 2400 ×
Voltage: 20 kV



Allergic reactions to starch are extremely rare and individuals apparently allergic to one particular starch may not experience adverse effects with a starch from a different botanical source.

LD_{50} (mouse, IP): 6.6 g/kg[22]

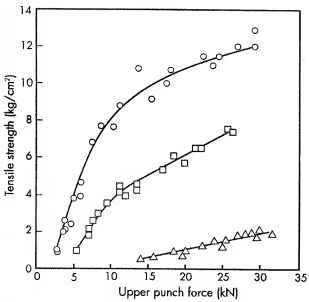


Figure 1: Compression characteristics of corn, potato and wheat starches.
□: Corn starch
○: Potato starch
△: Wheat starch
Tablet machine: Manesty F; speed: 50 per min; weight: 490–510 mg. Strength test: Diametral compression between flat-faced rams. Upper ram stationary, lower moving at 66 μm/s.

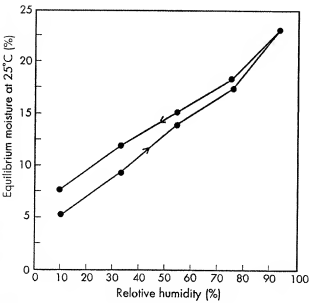


Figure 2: Sorption-desorption isotherm of corn starch. Anheuser Busch; Lot #67.

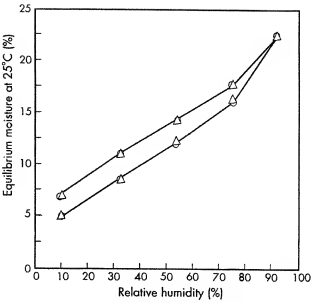


Figure 3: Sorption-desorption isotherm of wheat starch.
○: *Paygel 55* (Henkel Corp.; Lot #2917D)
△: *Aytex P* (Henkel Corp.; Lot #2919D)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosion.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m³ for total inhalable dust and 4 mg/m³ for respirable dust.[23]

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Amylopectin; α-amylose; starch, pregelatinized; starch, sterilizable maize.

Amylopectin

CAS number: [9037-22-3]
Comments: amylopectin is a branched D-glucan with mostly α-D-(1→4) and approximately 4% α-D-(1→6) linkages.
The EINECS number for amylopectin is 232-911-6.

α-Amylose

CAS number: [9005-82-7]
Comments: amylose is a linear (1→4)-α-D-glucan.

18 Comments

Note that corn starch is also known as maize starch and that tapioca starch is also known as cassava starch.

Whereas the USPNF 20 specifies that starch should be produced from corn, potato, tapioca, or wheat, the BP 2001

also permits starch to be produced from rice. In tropical and subtropical countries where these starches may not be readily available, the BP 2001 additionally permits the use of tapioca starch, subject to additional requirements.

Starches from different plant sources differ in their amylose/amylopectin ratio. For example, corn starch contains about 27% amylose, potato starch about 22%, and tapioca starch about 17%. In contrast, waxy corn starch contains almost entirely amylopectin, with no amylose. These differences modify the physical properties of the starches such that the various types may not be interchangeable in a given pharmaceutical application.

19 Specific References

1 York P. Studies of the effect of powder moisture content on drug release from hard gelatin capsules. *Drug Dev Ind Pharm* 1980; 6: 605–627.

2 Ingram JT, Lowenthal W. Mechanism of action of starch as a tablet disintegrant I: factors that affect the swelling of starch grains at 37°. *J Pharm Sci* 1966; 55: 614–617.

3 Patel NR, Hopponen RE. Mechanism of action of starch as a disintegrating agent in aspirin tablets. *J Pharm Sci* 1966; 55: 1065–1068.

4 Lowenthal W. Mechanism of action of tablet disintegrants. *Pharm Acta Helv* 1973; 48: 589–609.

5 Sakr AM, Kassem AA, Farrag NA. The effect of certain disintegrants on water soluble tablets. *Manuf Chem Aerosol News* 1973; 44(1): 37–41.

6 Shangraw RF, Wallace JW, Bowers FM. Morphology and functionality in tablet excipients for direct compression: part II. *Pharm Technol* 1981; 5(10): 44–60.

7 Kitamori N, Makino T. Improvement in pressure-dependent dissolution of trepibutone tablets by using intragranular disintegrants. *Drug Dev Ind Pharm* 1982; 8: 125–139.

8 Rudnic EM, Rhodes CT, Welch S, Bernardo P. Evaluation of the mechanism of disintegrant action. *Drug Dev Ind Pharm* 1982; 8: 87–109.

9 Kortke MK, Chueh H-R, Rhodes CT. Comparison of disintegrant and binder activity of three corn starch products. *Drug Dev Ind Pharm* 1992; 18: 2207–2223.

10 Faroongsarng D, Peck GE. Swelling and water reuptake of tablets. Part 3. Moisture sorption behavior of tablet disintegrants. *Drug Dev Ind Pharm* 1994; 20: 779–798.

11 Illum L, Fisher AN, Jabbal-Gill I, Davis SS. Bioadhesive starch microspheres and absorption enhancing agents act synergistically to enhance the nasal absorption of polypeptides. *Int J Pharm* 2001; 222: 109–119.

12 Henrist D, Van Bortel L, Lefebvre RA, Remon JP. *In vitro* and *in vivo* evaluation of starch based hot stage extruded double matrix systems. *J Control Release* 2001; 75: 391–400.

13 Palviainen P, Heinamaki J, Myllarinen P, *et al.* Corn starches as film formers in aqueous-based film coating. *Pharm Dev Technol* 2001; 6: 353–361.

14 Bromberg LE, Buxton DK, Friden PM. Novel peridontal drug delivery systems for treatment of periodontitis. *J Control Release* 2001; 71: 251–259.

15 Clausen AE, Bernkop-Schnurch A. Direct compressible polymethacrylic acid-starch compositions for site-specific drug delivery. *J Control Release* 2001; 75: 93–102.

16 Carr RL. Particle behaviour storage and flow. *Br Chem Eng* 1970; 15: 1541–1549.

17 Callahan JC, Cleary GW, Elefant M, *et al.* Equilibrium moisture content of pharmaceutical excipients. *Drug Dev Ind Pharm* 1982; 8: 355–369.

18 Wurster DE, Peck GE, Kildsig DO. A comparison of the moisture adsorption–desorption properties of corn starch, USP, and directly compressible starch. *Drug Dev Ind Pharm* 1982; 8: 343–354.

19 Weiner M, Bernstein IL. *Adverse Reactions to Drug Formulation Agents: A Handbook of Excipients*. New York: Marcel Dekker, 1989: 91–92.

20 Warshaw AL. Diagnosis of starch peritonitis by paracentesis. *Lancet* 1972; ii: 1054–1056.

21 Michaels L, Shah NS. Dangers of corn starch powder [letter]. *Br Med J* 1973; 2. 714.

22 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 3298.

23 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

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21 Author

G Rowley.

22 Date of Revision

10 March 2002.

Starch, Pregelatinized

1 Nonproprietary Names

BP: Pregelatinised starch
PhEur: Amylum pregelificatum
USPNF: Pregelatinized starch

2 Synonyms

Compressible starch; *Instastarch*; *Lycatab C*; *Lycatab PGS*; *Merigel*; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST 200*; *Spress B820*; *Starch 1500 G*; *Tablitz*; *Unipure LD*; *Unipure WG220*.

3 Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

4 Empirical Formula Molecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. The USPNF 20 does not specify the botanical origin of the original starch, but the PhEur 2002 (Suppl 4.1) specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch. *See also* Starch and Section 13.

5 Structural Formula

See Starch.

6 Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,[1,2] and disintegrant.[3]

In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression processes.[4–14] In such processes, pregelatinized starch is self-lubricating. However, when it is used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.[15]

Pregelatinized starch may also be used in wet granulation processes.[16] *See* Table I.

Table I: Uses of pregelatinized starch.

Use	Concentration (%)
Diluent (hard gelatin capsules)	5–75
Tablet binder (direct compression)	5–20
Tablet binder (wet granulation)	5–10
Tablet disintegrant	5–10

8 Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e., no 'maltese crosses' characteristic of the starch birefringence pattern. Examination of samples suspended in glycerin show characteristic forms depending upon the method of drying used during manufacture: either irregular chunks from drum drying or thin plates. Partially pregelatinized starch (e.g., *Starch 1500G* and *Sepistab ST200*) show rerention of birefringence patterns typical of unmodified starch granules.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for pregelatinized storch.

Test	PhEur 2002 (Suppl 4.1)	USPNF 20
Identification	+	+
pH (10% w/v slurry)	4.5–7.0	4.5–7.0
Iron	⩽20 ppm	⩽0.002%
Oxidizing substances	+	+
Sulfur dioxide	⩽50 ppm	⩽0.008%
Microbial limits	+	+
Loss on drying	⩽15.0%	⩽14.0%
Residue on ignition	—	⩽0.5%
Foreign matter	+	—
Sulfated ash	⩽0.6%	—
Organic volatile impurities	—	+

10 Typical Properties

Acidity/alkalinity: pH = 4.5–7.0 for a 10% w/v aqueous dispersion.
Angle of repose: 40.7° [6]
Compressibility: *see* Starch.
Density (bulk): 0.586 g/cm^3
Density (tapped): 0.879 g/cm^3
Density (true): 1.516 g/cm^3
Flowability: 18–23% (Carr compressibility index)[17]
Moisture content: pregelatinized maize starch is hygroscopic.[14,18,19] *See also* Figure 1.

Particle size distribution: 30–150 μm, median diameter 52 μm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149 μm); and less than 0.5% retained on a US #40 mesh (420 μm).
Solubility: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold-water-soluble matter for partially pregelatinized starch is 10–20%.
Specific surface area:
0.26 m^2/g (Colorcon)
0.18–0.28 m^2/g (Roquette Ltd)
Viscosity (dynamic): 8–10 mPa s (8–10 cP) for a 2% w/v aqueous dispersion at 25 °C.

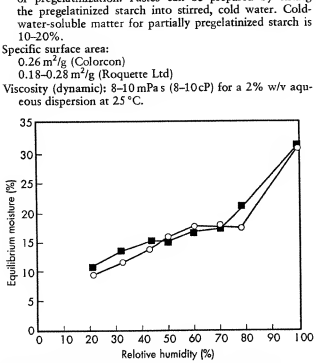

Figure 1: Pregelatinized starch sorption–desorption isotherm.
○: Sorption. ■: Desorption.

11 Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

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13 Method of Manufacture

Food-grade pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62–72 °C. Chemical additives that may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded, or drum-dried. In the last case, the dried material may be processed to produce a desired particle size range.

Pharmaceutical grades of fully pregelatinized starch use no additives and are prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where gelatinization and subsequent drying takes place. Partially pregelatinized starch is produced by subjecting moistened starch to mechanical pressure. The resultant material is ground and the moisture content is adjusted to specifications.

14 Safety

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of massive amounts of pregelatinized starch may be harmful.

See Starch for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[20]

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Starch; starch, sterilizable maize.

18 Comments

A low-moisture grade of pregelatinized starch, *Starch 1500 LM* (Colorcon), containing less than 7% of water, specifically intended for use as a diluent in capsule formulations is commercially available.[15]

Sepistab ST200 is described as an agglomerate of starch granules consisting of native and pregelatinized corn starch.[21]

19 Specific References

1 Small LE, Augsburger LL. Aspects of the lubrication requirements for an automatic capsule filling machine. *Drug Dev Ind Pharm* 1978; 4: 345–372.
2 Mattson S, Nyström C. Evaluation of critical binder properties affecting the compactability of binary mixtures. *Drug Dev Ind Pharm* 2001; 27: 181–194.
3 Rudnic EM, Rhodes CT, Welch S, Bernardo P. Evaluations of the mechanism of disintegrant action. *Drug Dev Ind Pharm* 1982; 8: 87–109.
4 Manudhane KS, Contractor AM, Kim HY, Shangraw RF. Tableting properties of a directly compressible starch. *J Pharm Sci* 1969; 58: 616–620.
5 Underwood TW, Cadwallader DE. Influence of various starches on dissolution rate of salicylic acid from tablets. *J Pharm Sci* 1972; 61: 239–243.
6 Bolhuis GK, Lerk CF. Comparative evaluation of excipients for direct compression. *Pharm Weekbl* 1973; 108: 469–481.
7 Sakr AM, Elsabbagh HM, Emara KM. Sta-Rx 1500 starch: a new vehicle for the direct compression of tablets. *Arch Pharm Chem (Sci)* 1974; 2: 14–24.
8 Schwartz JB, Martin ET, Dehner EJ. Intragranular starch: comparison of starch USP and modified cornstarch. *J Pharm Sci* 1975; 64: 328–332.
9 Rees JE, Rue PJ. Work required to cause failure of tablets in diametral compression. *Drug Dev Ind Pharm* 1978; 4: 131–156.
10 Shangraw RF, Wallace JW, Bowers FM. Morphology and functionality in tablet excipients for direct compression: part II. *Pharm Technol* 1981; 5(10): 44–60.

11 Chilamkurti RW, Rhodes CT, Schwartz JB. Some studies on compression properties of tablet matrices using a computerized instrumental press. *Drug Dev Ind Pharm* 1982; 8: 63–86.
12 Malamataris S, Goidas P, Dimitriou A. Moisture sorption and tensile strength of some tableted direct compression excipients. *Int J Pharm* 1991; 68: 51–60.
13 Iskandarani B, Shiromani PK, Clair JH. Scale-up feasability in high-shear mixers: determination through statistical procedures. *Drug Dev Ind Pharm* 2001; 27: 651–657.
14 Shiromani PK, Clair J. Statistical comparison of high-shear versus low-shear granulation using a common formulation. *Drug Dev Ind Pharm* 2000; 26: 357–364.
15 Colorcon Technical literature: *Starch 1500*. 1997.
16 Jaiyeoba KT, Spring MS. The granulation of ternary mixtures: the effect of the stability of the excipients. *J Pharm Pharmacol* 1980; 32: 1–5.
17 Carr RL. Particle behaviour storage and flow. *Br Chem Eng* 1970; 15: 1541–1549.
18 Callahan JC, Cleary GW, Elefant M, *et al*. Equilibrium moisture content of pharmaceutical excipients. *Drug Dev Ind Pharm* 1982; 8: 355–369.
19 Wurster DE, Peck GE, Kildsig DO. A comparison of the moisture adsorption–desorption properties of corn starch USP, and directly compressible starch. *Drug Dev Ind Pharm* 1982; 8: 343–354.
20 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.
21 Seppic. Technical Literature: *Sepistab ST200*. 1997.

20 General References

Monedeero Perales MC, Munoz-Ruiz A, Velasco-Antequera MV, *et al*. Comparative tableting and microstructural properties of a new starch for direct compression. *Drug Dev Ind Pharm* 1996; 22: 689–695.
Rees, JH, Tsardaka KD. Some effects of moisture on the viscoelastic behavior of modified starch during powder compaction. *Eur J Pharm Biopharm* 1994; 40: 193–197.
Roquette Frères. Technical literature: *Lycatab PGS*. 2001.
Sanghvi PP, Collins CC, Shukla AJ. Evaluation of Preflo modified starches as new direct compression excipients I: tabletting characteristics. *Pharm Res* 1993; 10: 1597–1603.

21 Author

G Rowley.

22 Date of Revision

13 June 2002.

Starch, Sterilizable Maize

1 Nonproprietary Names

USP: Absorbable dusting powder

2 Synonyms

Bio-sorb; double-dressed, white maize starch; *Fluidamid R444P*; *Keoflo ADP*; *Meritena*; modified starch dusting powder; *Pure-Dent B851*; starch-derivative dusting powder; sterilizable corn starch.

3 Chemical Name and CAS Registry Number

Sterilizable maize starch

4 Empirical Formula Molecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Sterilizable maize starch is a modified corn (maize) starch that may also contain up to 2.0% of magnesium oxide.

See also Starch.

5 Structural Formula

See Starch.

6 Functional Category

Lubricant for surgeons' and examination gloves; vehicle for medicated dusting powders.

7 Applications in Pharmaceutical Formulation or Technology

Sterilizable maize starch is a chemically or physically modified corn (maize) starch that does not gelatinize on exposure to moisture or steam sterilization. Sterilizable maize starch is primarily used as a lubricant for examination and surgeons' gloves. It is also used as a vehicle for medicated dusting powders.

8 Description

Sterilizable maize starch occurs as an odorless, white, free-flowing powder. Particles may be rounded or polyhedral in shape.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sterilizable maize starch.

Test	USP 25
Identification	+
Stability to autoclaving	+
Sedimentation	+
pH (1 in 10 suspension)	10.0–10.8
Loss on drying	≤12%
Residue on ignition	≤3%
Magnesium oxide	≤2.0%
Heavy metals	≤0.001%

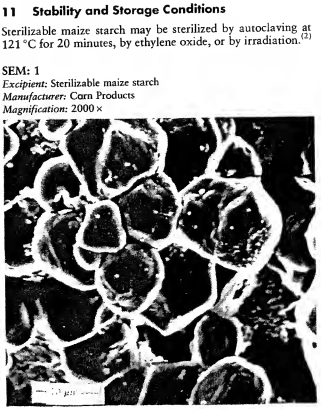
10 Typical Properties

Acidity/alkalinity: pH = 9.5–10.8 for a 10% w/v suspension at 25 °C.
Density: 1.48 g/cm^3
Density (bulk): 0.47–0.59 g/cm^3
Density (tapped): 0.64–0.83 g/cm^3
Flowability: 24–30% (Carr compressibility index)[1]
Moisture content: 10–15%
Particle size distribution: 6–25 µm; median diameter is 16 µm.
Solubility: very slightly soluble in chloroform and ethanol (95%); practically insoluble in water.
Specific surface area: 0.50–1.15 m^2/g

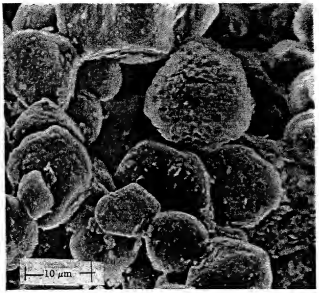
11 Stability and Storage Conditions

Sterilizable maize starch may be sterilized by autoclaving at 121 °C for 20 minutes, by ethylene oxide, or by irradiation.[2]

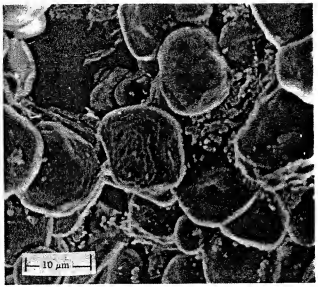
SEM: 1
Excipient: Sterilizable maize starch
Manufacturer: Corn Products
Magnification: 2000×



SEM: 2
Excipient: Sterilizable maize starch
Manufacturer: Biosorb
Magnification: 2000×



SEM: 3
Excipient: Sterilizable maize starch
Manufacturer: J & W Starches Ltd
Magnification: 2000×



Sterilizable maize starch should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

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13 Method of Manufacture

Corn starch (maize starch) is physically or chemically modified by treatment with either phosphorus oxychloride or epichlorhydrin so that the branched-chain and straight-chain starch polymers crosslink. Up to 2.0% of magnesium oxide may also be added to the starch.

See also Starch.

14 Safety

Sterilizable maize starch is primarily used as a lubricant for surgeons' gloves and as a vehicle for topically applied dusting powders.

Granulomatous reactions and peritonitis at operation sites have been attributed to contamination with surgical glove powders containing sterilizable maize starch.[3,4] The use of excessive quantities of sterilizable maize starch on surgeons' gloves should therefore be avoided.

See also Starch.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[5]

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets and topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Starch; starch, pregelatinized.

18 Comments

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19 Specific References

1 Carr RL. Particle behaviour storage and flow. *Br Chem Eng* 1970; 15: 1541–1549.
2 Kelsey JC. Sterilization of glove powder by autoclaving. *Mon Bull Minist Health* 1962; 21: 17–21.
3 Neely J, Davis JD. Starch granulomatosis of the peritoneum. *Br Med J* 1971; 3: 625–629.
4 Michaels L, Shah NS. Dangers of corn starch powder [letter]. *Br Med J* 1973; 2: 714.
5 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*, Sudbury: Health and Safety Executive, 2002.

20 General References

El Saadany RMA, El Saadany FM, Foda YH. Degradation of corn starch under the influence of gamma irradiation. *Staerke* 1976; 28: 208–211.
Greenwood CT. The thermal degradation of starch. *Adv Carbohydr Chem Biochem* 1967; 22: 483–515.
Greenwood CT. Starch. *Adv Cereal Sci Technol* 1976; 1: 119–157.

21 Author

G Rowley.

22 Date of Revision

13 June 2002.